REMARKS

This communication is responsive to the Office Action dated November 6, 2009. Applicant respectfully requests entry of the foregoing amendments and reconsideration of the application in view of the foregoing amendment and the following remarks.

I. Status of the claims

Claims 30, 32, 33, 37 and 40 were previously withdrawn pursuant to an election of species. Applicant respectfully request rejoinder and examination of the withdrawn claims upon identification of allowable subject matter in generic or linking claims.

Claims 1-28 were previously cancelled, and claim 34 is now cancelled and its subject matter incorporated into claims 29 and 30.

Claim 29 is amended to specify that the interleukin-6 (IL-6) antagonist is an antibody against interleukin (IL-6) receptor. Claim 30 is also amended to parallel the amendments made to claim 29, thus facilitating rejoinder and allowance of withdrawn claim 30 upon allowance of the elected species. These amendments incorporate subject matter from claim 34, now cancelled. Claims 35-38 and 41, which previously depended from claim 34, are also amended to now depend from claim 29.

No new matter is added. The foregoing amendments are made solely to advance prosecution and not in acquiescence to any rejection or objection. Applicants reserve the right to pursue any subject matter removed by amendment in continuing applications with the same right of priority as the present application.

Following entry of the foregoing amendments, claims 29-33 and 35-42 are pending, and claims 29, 31, 35, 36, 38, 39, 41 and 42 are under examination. Claim 29 is the sole independent claim under examination.

II. Finality is premature

The rejection

The present rejections under 35 U.S.C. §§ 102, 103 are over new art that is not previously of record. The finality of this Action proceeds from the assertion that "Applicant's

amendment necessitate the new ground(s) of rejection presented in this Office Action." Office Action at page 4. Applicant believes that finality is premature.

The amendments

Claim 29 was previously amended to delete "preventing" which was alleged to exceed the enablement provided by the specification. Previous rejections under 35 U.S.C. §§ 102, 103 were overcome by attorney argument, and not in view of the deletion of "preventing."

The amendments did not necessitate finality

MPEP § 706.07(a) states that:

> Under present practice, second or any subsequent actions on the merits shall be final, ***except where the examiner introduces a new ground of rejection that is neither necessitated by applicant's amendment of the claims***, nor based on information submitted in an information disclosure statement filed during the period set forth in 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p).
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> . . . .
>
> ***[A] second or any subsequent action on the merits*** in any application or patent undergoing reexamination proceedings ***will not be made final if it includes a rejection, on newly cited art,*** other than information submitted in an information disclosure statement filed under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p), ***of any claim not amended by applicant or patent owner in spite of the fact that other claims may have been amended to require newly cited art***.

Emphasis supplied. Because the amendment must "necessitate" the rejection, there is an implicit requirement for a *nexus* between the newly cited art and the amendment. The mere existence of an amendment does not create such a nexus. There is no nexus between the amendment and the newly cited art: in this case the new art could have, and should have, been asserted and made of record in the previous rejection.

Moreover, finality is premature under the principles espoused at MPEP § 706.07, that

> ***Before final rejection is in order a clear issue should be developed between the examiner and applicant.*** To bring the

> prosecution to as speedy conclusion as possible and at the same time to deal justly by both the applicant and the public, ***the invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied; and in reply to this action the applicant should amend with a view to avoiding all the grounds of rejection and objection.***
> ....

Because the "invention as disclosed and claimed should be thoroughly searched in the first action and the references fully applied," the citation of new references that could have been applied to the previous claims should not be a basis for final rejection. Such premature finality also does not permit the Examiner and Applicant to develop "a clear issue" for consideration, nor meet the goal of bringing prosecution to a speedy conclusion and deal justly with Applicant and the public.

Relief sought

The prematurity of a final rejection is being raised while the application is pending before the Examiner, and is timely under MPEP § 706.07. Because the present Request for Continued Examination is necessitated by the premature finality, Applicant requests a refund of the RCE fees.

III. Rejections under 35 U.S.C. § 102

The cited art does not anticipate the present claims

At pages 2-3 of the Office Action, claim 29 is rejected under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 7,612,182 to Giles-Komar ("Giles-Komar") or U.S. Patent No. 5,843,994 to Samid ("Samid"). Both references allegedly teach that a list of diseases (among which includes "vasculitis") may be treated by administration of (a) antibodies against IL-6 (Giles-Komar) or (b) phenylacetic acid (Samid). Applicant respectfully traverses. Solely to advance prosecution, however, claim 29 has been amended to recite "an antibody against IL-6 receptor," which is not taught in either Giles-Komar or Samid. Accordingly, Giles-Komar and Samid do not anticipate claim 29.

At page 2 of the Office Action, claims 29, 34-36, 38, 39, 41 and 42 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by U.S. Patent Application Publication No. 2006/0251653 to Okuda ("Okuda"). Applicant respectfully traverses.

First, Okuda is not prior art under 35 U.S.C. § 102(a). The present application claims priority to Japanese Application No. 2003-0423517, filed December 19, 2003. The application's priority date is prior to the November 9, 2006, publication date of U.S. 2006/0251653, and is also prior to the November 11, 2004, publication date of WO 2004/096273, the equivalent PCT publication of the Okuda reference.

Okuda is also not prior art under 35 U.S.C. § 102(e). For purposes of 35 U.S.C. § 102(e) prior art, Okuda's earliest date is the filing date of the PCT, April 28, 2004, because the foreign priority date (April 28, 2003) is unavailable under 35 U.S.C. § 102(e). *See* 35 U.S.C. § 102(e), *see also* MPEP § 2136.03. As the present application is entitled to its foreign priority date of December 19, 2003, for purposes of defeating 35 U.S.C. § 102(e) art, and such priority date is prior to April 28, 2004, Okuda is not prior art under 35 U.S.C. § 102(e).

The cited art also is not enabling

A claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). The cited art also does not anticipate because it does not describe the claimed invention with sufficient enabling detail to place the public in possession of the invention.

Giles-Komar and Samid list vasculitis as merely one of a large number of possible diseases which may be modulated or treated, and do not demonstrate that an anti-IL-6 antibody or phenylacetic acid derivatives are useful for treating vasculitis. More so, Giles-Komar and Samid list do not enable anti-IL-6 *receptor* antibody for treatment of vasculitis. Okuda describes a combined use of an IL-6 antagonist and an immunosuppressant, but does describe the usefulness of an IL-6 antagonist *alone* for treating vasculitis.

The requirement for the prior art to provide an enabling disclosure is particularly acute in view of the great unpredictability in the field, as demonstrated by the prior art. It was well known in the art that the cytokine network is complex and interrelated, defeating the ability to extrapolate from correlation to causation, and further to treatment.

Bellomo ("The cytokine network in the critically ill" *Anaesthesia and Intensive Care* 20 (3) 288-302 (1992)(Exhibit 1)) describes that since the cytokine network is extraordinarily complex "he or she should grasp the fundamental rules of this biological alphabet and thus avoid the oversimplifications that may accompany the future clinical use of these polypeptides and of their antagonists." Bellomo, page 294, col. 2. Cytokine networks, of which Il-6 is one element, are characterized by:

(1) Pleiotropy (a cytokine exhibits multiple biological actions);

(2) Redundancy (a plurality of cytokines exhibit the same action on the same cell)

(3) A plurality of cytokines are involved in the same cell line depending on the process of differentiation and growth.

The complexity in cytokine networks has been shown for several cytokines, including IL-6. For example, Ulich ("Intratracheal injection of endotoxin and cytokines" *Am. J. Pathol.* 138(5): 1097-1101 (1991)(Exhibit 2)) report in the abstract that "Interleukin-6 also is shown to be endogenously upregulated within the lung after intratracheal challenge with endotoxin, providing evidence that 1L-6 may represent an endogenous negative feedback mechanism to inhibit endotoxin-initiated cytokine-mediated acute inflammation." Thus, the increase in IL-6 levels with disease was not evidence of causation but the complete opposite, as part of a mechanism to *decrease* acute inflammatory processes. *See also* page 1100, second column ("Host-derived IL-6 is upregulated locally after challenge with LPS and may act as an endogenous negative feedback mechanism to inhibit the LPS-initiated IL-l and TNF-mediated acute inflammatory process").

Similar effects have been observed with other cytokines. For example, Murata ("Possible implications of cytokines in the pathophysiology of acute pancreatitis" *Saishin Igaku* (in English, *New Medicine*) 47(11): 49-56 (1992) (Exhibit 2)) describes at page 10, lines 10 to 23 of the English translation that:

> Administration of anti-TNF antibody In cerulein-induced pancreatitis augmented not only pancreatic edema but also pulmonary lesions. The inhibition of the TNF action by the pretreatment prevents from transmitting the abnormality called cerulein-induced pancreatitis to the body's defensive system. In other words, when rats themselves try to complete the inflammatory reaction by their own defense system, the first step signal, TNF cannot transmit its signal to the next one. As the result, anti-inflammatory reactions cannot be taken place so that pancreatic inflammation becomes severe, and pancreatic inflammation itself is aggravated more by severe local tissue lesions. Thus it is considered that pulmonary lesions were developed by a cytokine network without a TNF-mediated pathway.

This reference also describes the many overlapping complexities in cytokine networks. *See* especially, English translation, page 12, lines 2-9, and page 13, line 3-7.

It follows that merely listing vasculitis as one disease among many that are associated with IL-6 is neither (a) evidence of causation nor (b) evidence that decreasing or blocking IL-6 with an antagonist would likewise treat vasculitis without clear evidence that such an antagonist is effective for that *specific* disease. Accordingly, the disclosure of the cited art is insufficiently enabled to sustain the present rejections under 35 U.S.C. § 102.

Summary

The present claims recite a method of treating vasculitis comprising administering an antibody against interleukin (IL-6) receptor to a subject in need thereof. Giles-Komar and Samid do not anticipate because they not teach an antibody against IL-6 receptor. Okuda does not anticipate because it is not prior art under 35 U.S.C. § 102(a) or (e). Giles-Komar, Samid and Okuda also do not anticipate because they do not describe the claimed invention with sufficient enabling detail to place the public in possession of the invention, in view of the complexity and unpredictability in the field.

Applicant respectfully requests reconsideration and withdrawal of the rejections under 35 U.S.C. § 102 of claims 29, 35-36, 38, 39, 41 and 42.

IV. Rejections under 35 U.S.C. § 103

At pages 3-4 of the Office Action, claim 31 is rejected under 35 U.S.C. § 103(a) as allegedly rendered obvious by any of Giles-Komar, Samid or Okuda in view of Hirohata *et al.* "Elevation of cerebrospinal fluid interleukin-6 activity in patients with vasculitides and central nervous system involvement" *Clin. Immunol and Immunopath* 66:225-229 (1993) ("Hirohata"). Applicant respectfully traverses.

The obviousness rejection proceeds from the anticipation rejection of claims 29, 35-36, 38, 39, 41 and 42, which has been overcome. Moreover, the combination with Hirohata does not remedy the defects of the primary references. Even though Hirohata describes the relationship between elevated IL-6, polyarteritis nodosa and vasculitis, it does not follow that IL-6 is causative of the disease, or that the disease could be treated by an antagonist to IL-6 or, more specifically, by an antibody against the IL-6 receptor. Applicant respectfully requests reconsideration and withdrawal of the obviousness rejection.

CONCLUSION

Applicant believes that all rejections and objections are overcome, and that all claims under examination are allowable. Applicant further request that the Examiner rejoin and examine withdrawn claims 30, 32, 33, 37 and 40.

The Examiner is invited to contact the undersigned if it believed that such communication would facilitate examination of the application.

The Commissioner is hereby authorized to credit any overpayment, or charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or any missing fees, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date May 3, 2010

By /SElliott/

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4726
Facsimile: (202) 672-5399

Simon J. Elliott, Ph.D. J.D.
Attorney for Applicant
Registration No. 54,083